Cerebral Cortex, 2018; 1–12

doi: 10.1093/cercor/bhy048
Original Article

ORIGINAL ARTICLE

Distinct Roles for the Cerebellum, Angular Gyrus, and Middle Temporal Gyrus in Action–Feedback Monitoring

Bianca M. van Kemenade[1], B. Ezgi Arikan[1], Kornelius Podranski[1,2], Olaf Steinsträter[1], Tilo Kircher[1] and Benjamin Straube [1]

[1]Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Rudolf-Bultmann-Straße 8, 35039 Marburg, Germany and [2]Technische Hochschule Mittelhessen, Wiesenstraße 14, 35390 Gießen, Germany

Address correspondence to Bianca M. van Kemenade, Rudolf-Bultmann-Straße 8, 35039 Marburg, Germany. Email: vankemen@med.uni-marburg.de

Abstract

Action–feedback monitoring is essential to ensure meaningful interactions with the external world. This process involves generating efference copy-based sensory predictions and comparing these with the actual action-feedback. As neural correlates of comparator processes, previous fMRI studies have provided heterogeneous results, including the cerebellum, angular and middle temporal gyrus. However, these studies usually comprised only self-generated actions. Therefore, they might have induced not only action-based prediction errors, but also general sensory mismatch errors. Here, we aimed to disentangle these processes using a custom-made fMRI-compatible movement device, generating active and passive hand movements with identical sensory feedback. Online visual feedback of the hand was presented with a variable delay. Participants had to judge whether the feedback was delayed. Activity in the right cerebellum correlated more positively with delay in active than in passive trials. Interestingly, we also observed activation in the angular and middle temporal gyri, but across both active and passive conditions. This suggests that the cerebellum is a comparator area specific to voluntary action, whereas angular and middle temporal gyri seem to detect more general intersensory conflict. Correlations with behavior and cerebellar activity nevertheless suggest involvement of these temporoparietal areas in processing and awareness of temporal discrepancies in action-feedback monitoring.

Key words: action, efference copy, fMRI, prediction error, temporal mismatch

Introduction

In order to establish meaningful interactions with the external world, it is essential that we are able to understand the relation between our actions and the resulting sensory consequences. This action-feedback monitoring is an important process that aids in motor learning and distinguishing self-generated from externally generated stimuli. It is thought that action-feedback monitoring is based on an internal forward model, which uses efference copies to generate predictions about the sensory consequences of our actions (Sperry 1950; von Holst and Mittelstaedt 1950; Miall and Wolpert 1996; Wolpert and Flanagan 2001). These predictions are then compared with the actual sensory feedback, resulting in prediction errors in case of a mismatch (Wolpert and Flanagan 2001; Wolpert et al. 2011). Through this comparative mechanism, we are able to monitor our actions, distinguish them from externally generated actions, and update our predictions when needed (Wolpert and Ghahramani 2000; Blakemore and Sirigu 2003).

Many studies have explored which brain areas would qualify as "comparator areas", comparing predicted from actual sensory outcomes using the efference copy and generating prediction errors in case of a mismatch. These studies have often

© The Author(s) 2018. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

introduced temporal or spatial deviations between action and feedback, using either rather abstract feedback such as a cursor or a dot on a screen (Diedrichsen et al. 2005; David et al. 2007; Schlerf et al. 2012; Straube, Schülke, Drewing, et al. 2017; Straube, van Kemenade, Arikan, et al. 2017; van Kemenade et al. 2017), or more natural feedback such as video recordings of the hand (Leube, Knoblich, Erb, Grodd, et al. 2003; Leube, Knoblich, Erb, Kircher et al. 2003; Farrer et al. 2008). Until now, the neural correlates of comparative processes are still unclear, since results have been heterogeneous, attributing comparative functions to various brain areas. There is considerable evidence in support of the hypothesis that the cerebellum is the locus of comparative processes in the human brain. First of all, some fMRI studies have found that activity in the cerebellum is significantly higher in trials with sensory errors than trials without error (Diedrichsen et al. 2005; Schlerf et al. 2012), or that activity in the cerebellum correlates with the magnitude of temporal deviations between action and feedback (Blakemore et al. 2001). Furthermore, patient studies have repeatedly shown that cerebellar patients are impaired at updating predictions about sensory action consequences (Tseng et al. 2007; Synofzik, Lindner, et al. 2008; Roth et al. 2013). However, many other studies have rather found evidence for the involvement of the parietal cortex, in particular the angular gyrus and superior parietal lobule, in the comparison of predicted with actual consequences of one's own action. For example, parietal areas have been found to show increased activity during mismatches between actions and sensory feedback (Leube, Knoblich, Erb, Kircher, et al. 2003; David et al. 2007; Farrer et al. 2008; van Kemenade et al. 2017). Furthermore, it has been reported that a lesion in this area resulted in disrupted sensorimotor integration (Wolpert et al. 1998). The angular gyrus also seems to code for action awareness, since this region was more active when participants were aware of a discrepancy between predicted and actual feedback, as compared to when they were not aware of the discrepancy (Farrer et al. 2008). Congruent with these findings are reports that the angular gyrus is active when the sense of agency–the feeling that it is me who caused the action—is violated (Farrer and Frith 2002; Farrer et al. 2008; Nahab et al. 2011; Yomogida et al. 2010). Indeed, when the function of the parietal lobe was impaired through transcranial magnetic stimulation, agency processing was disrupted (Khalighinejad and Haggard 2015). In addition to the studies on the cerebellum and parietal cortex, it has been reported that temporal areas may be involved in the comparison between predicted and actual action feedback as well. Using visual feedback that was either presented in line with participants' movement, or with a variable delay, Leube and colleagues found that activity in the superior temporal sulcus correlated positively with the amount of delay (Leube, Knoblich, Erb, Grodd, et al. 2003). In a later study with schizophrenia patients and healthy controls, they found a region in the middle temporal cortex that showed a similar correlation with delay in healthy controls (Leube et al. 2010). In addition, the extrastriate body area (EBA), located in the middle temporal gyrus, has been found to be more active for incongruent compared to congruent action feedback (David et al. 2007).

Thus, the results reported in the literature are quite heterogeneous. It should be noted that none of the mentioned studies directly compared self-generated with externally generated feedback in order to study comparative processes. However, when inserting deviations between action and feedback, one does not only induce prediction errors, but also general mismatches between the different signals. For example, when hand movements are recorded and displayed with a delay, there is not only a mismatch between predicted and actual sensory consequences, but also a mismatch between the temporal occurrence of tactile or proprioceptive signals and the visual feedback. It has been shown that some of the previously mentioned candidate comparator areas in the temporal and parietal cortex can also be activated simply by intersensory conflicts (Shimada et al. 2005), showing no difference between active or passive conditions (Balslev et al. 2006; Tsakiris et al. 2010). In addition, transcranial magnetic stimulation (TMS) over the temporoparietal junction can abolish intersensory conflict (Papeo et al. 2010). In the current study, we aimed to resolve the heterogeneity in the literature by testing comparative processes with the use of a custom-made passive movement device. With this device, we could induce both active and passive movements, whilst keeping all sensory feedback equal. In this way, we were able to tease apart which brain areas are involved in detecting intersensory conflict in general ("intersensory conflict detection" areas), and which areas are specific to voluntary action, i.e., comparing predicted action consequences, generated using the efference copy, with actual action consequences ("comparator" areas). In addition, we wanted to investigate whether multisensory action consequences are processed differently than unisensory action consequences. So far, only few studies have investigated multisensory action predictions. A behavioral study from our group suggested that the forward model creates multisensory action predictions (van Kemenade et al. 2016), supported by later fMRI studies (Straube, van Kemenade, Arikan, et al. 2017; van Kemenade et al. 2017). However, whether the same brain area is involved in comparative processes for both unimodal and bimodal action consequences, specifically for voluntary action, is unknown. In the current fMRI study, we included real-time and delayed visual feedback of active and passive movements, to investigate (1) which brain area functions as a comparator area specifically for voluntarily generated consequences, (2) which brain area functions as an area generally matching sensory (e.g., visual, tactile and proprioceptive) signals, regardless of the presence of efference copy, and (3) whether there are any differences in such comparative mechanisms between unimodal and bimodal action consequences (when additional auditory information is provided).

Materials and Methods

Participants

Twenty-three right-handed healthy participants took part in the fMRI experiment. All participants had normal or corrected-to-normal vision and normal hearing. Furthermore, they reported no history of psychiatric or neurological disorders, and no current use of psychoactive medications. Right-handedness was confirmed by the Edinburgh Handedness Inventory (Oldfield 1971). The experiment was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Three participants had to be excluded due to excessive head movement ($n = 1$) or technical issues ($n = 2$), resulting in a final sample of 20 participants (9 females, age = 26 ± 3.24). From two participants, one run each had to be excluded due to technical issues. All participants were trained in a behavioral training session prior to scanning. Of the originally trained 24 participants, one participant was not selected for the fMRI experiment based on their performance in the training session (see Stimuli and Procedure).

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

Equipment

A custom-made MRI-compatible passive movement device (PMD) was used for the execution of both active and passive movements. The device comprised a grip that participants could move actively in active trials. In the passive condition, the grip was moved automatically, so that the hand of the participant, loosely holding the grip, was being moved passively from left to right and back. Since this grip had to be used in all conditions, the movements were restricted and could only follow a predefined path (Fig. 1A). The grip of the movement device was attached to a cylinder that only allowed circular motion. The starting/ending point (on the left side) and turning point (on the right side) were fixed. The angle between starting/ending and turning point was ~30°. Since this trajectory was fixed, the only variable that could change was the speed with which the participants moved the grip in the active conditions, leading to potential variability in the movement durations. Posthoc analyses showed however that there was no significant difference in movement durations between active and passive conditions (see Discussion–Behavioral Results). The device was driven pneumatically with compressed air (6 bar) by a compressor, which was located in a separate control room during the experiment. Approximate force used when the device worked automatically was 20 N. Active and passive movements were recorded by a high-speed, MRI-compatible camera (MRC High Speed, MRC Systems GmbH, Heidelberg, Germany; refresh rate: ~4 ms). The video recordings were shown to the participants on a screen. Variable delays (0, 83, 167, 250, 333, or 417 ms), were introduced between the camera images and the actual movements. This delay range was applied successfully in our previous experiments (van Kemenade et al. 2016, 2017; Schmalenbach et al. 2017; Straube, Schülke, Drewing, et al. 2017; Straube, van Kemenade, Arikan, et al. 2017). In bimodal trials, auditory stimuli were added in the form of beeps (sine wave of 440 Hz) for a duration of 500 ms. The onset of the beep was coupled to the onset of the movement, with the same delay as the visual image. In order to detect when the participant started to move, infrared LEDs were attached to the device. These LEDs were not visible to the participant, but only visible to our infrared sensitive camera. Four LEDs were stationary to detect the absolute position of the device, the fifth moved with the grip to detect the grip's relative movement. An algorithm written specifically for this study was applied to the camera images to determine movement onset, which was used to correctly couple a tone to the movement in bimodal trials. The algorithm monitors the complete movement (current angle of the PMD) in real time. The procedure described below explains how the onset is derived from this data. The algorithm identified the location of the LEDs based on their brightness and relative distance to each other. It determined the spatial location of the moving LED, and calculated the difference in angle between the current location of the moving LED and its starting position. At each new incoming frame, the algorithm calculated whether there was a change in angle. When the position of the moving LED exceeded the threshold of 1°, it was marked as a potential movement onset. Two additional frames were analyzed to ensure that it was a true movement onset (requiring an increase of at least 0.5° per frame), and not wiggling around the starting position. With a rate of one frame per 4 ms, it thus took no longer than 12 ms to detect movement onset, and play a tone in bimodal trials. All equipment was controlled by custom written software running on a Personal Computer (Dell Optiplex 9020).

Stimuli and Procedure

Participants held the grip of the custom-made passive movement device throughout the whole experiment. During active blocks, they were asked to make hand movements by extending and flexing their wrist, moving the grip from the left to the right and back. During passive blocks, they were instructed to hold the grip loosely, keeping the hand as relaxed as possible. The active and passive hand movements were recorded by a high-speed, MRI compatible camera and displayed with a variable delay on a screen, visible to the participants. The task for the participants was to report whether they detected a delay between the displayed hand movement and their actual hand movement. The device and visual feedback were aligned and corresponded to

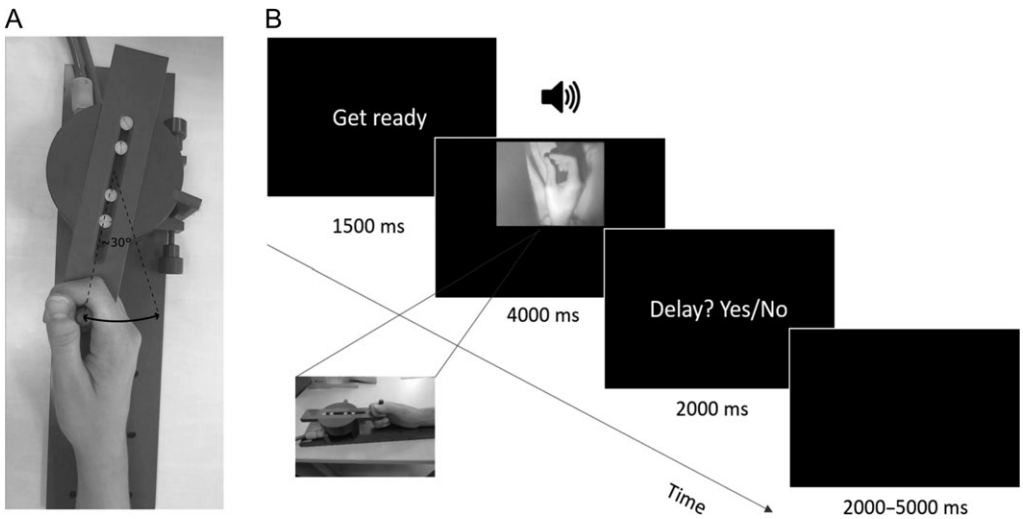

Figure 1. Setup and paradigm. (A) Passive movement device. Participants hold the grip and make left-right wrist movements in a fixed trajectory with an angle of ~30°. The grip can also be moved automatically with air pressure, moving the participant's hand in passive conditions. (B) Example of a bimodal trial. After the written cue, the camera was turned on, and participants either made an active movement or let their hand be moved by the device, depending on the block type. In bimodal trials, a tone was additionally presented, with its onset coupled to the onset of the movement. After the camera image was switched off, participants were asked to report whether they thought the visual feedback was delayed.

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

the participants' viewpoint. The participants could not see their own hand during the experiment, only the videos of their hand.

The procedure during the experiment was as follows. Each scanning run was divided into an active and a passive block, counterbalanced for each run. Each block started with the written instruction "Active block" or "Passive block", displayed for 4 s against a black background. This instruction was valid for the following 24 trials of that block. Each trial started with a written cue ("Ready") displayed for 1.5 s against a black background, to alert participants that the trial was about to start (Fig. 1*B*). In active blocks, this meant that participants should prepare to make their hand movement as soon as the camera was turned on. In passive blocks, this meant that participants should prepare to have their hand moved by the device as soon as the camera was turned on. The onset of the passive movement was jittered (500–1500 ms). After the disappearance of the cue, the camera image was shown for a duration of 4 s. During this time, participants either made their active movement or let their hand be moved by the device, depending on the block type. When they arrived back in the starting position on the left, they had to wait until the camera image disappeared. Right after, the question "Delay? Yes/No" appeared on the screen, and participants were allowed to answer whether they detected a delay or not using their left index and middle finger (key assignment counterbalanced across subjects). After a jittered intertrial interval (2, 3, 4, or 5 s), the next trial started. In half of the trials, only visual feedback was shown. In the other half of the trials, both visual and auditory feedback was presented. Unimodal and bimodal trials were randomized across each block. Each run contained two trials per delay per condition, leading to 12 unimodal and 12 bimodal trials for each block (active/passive), and thus to 48 trials per run. There were 5 runs in total for each participant. Each movement was monitored online and recorded to ensure compliance with instructions, and for posthoc analysis of movement durations.

Prior to scanning, participants were invited to a behavioral training session in order to familiarize themselves with the equipment and the task. In this training session, they were first shown how to make the required movements with the device. Then, they were briefly trained with a metronome to perform the movement at a constant pace. This was done to reduce differences between active and passive conditions, as the trained speed resembled the speed of passive movements. Furthermore, it would reduce differences between participants, since some participants would naturally move the device quicker or with more force than others. After the training with the metronome, participants were shown one trial for each condition without delay as an example, to get used to the trial sequence. Then, they performed one active training run and one passive training run of 8 trials each (4 without delay, 4 with the maximum delay of 417 ms, half of which unimodal, half of which bimodal), in which they received feedback about their delay detection performance. Lastly, they completed 3 runs that were equal to the main experimental runs in the scanning sessions. These runs did not include feedback about their performance. A curtain was used to obscure the view of the hand throughout the whole training session. Only participants with a detection rate of less than 50% at the 0 ms delay and a detection rate of at least 50% at the 417 ms delay were invited to the fMRI study. Only one subject did not meet these criteria.

Functional Data Acquisition

Functional MRI data were acquired using a 3 T TIM Trio scanner (Siemens, Erlangen, Germany), using a 12-channel head-coil. A gradient echo EPI sequence was used (TR: 1650 ms, TE: 25 ms, flip angle: 70°, slice thickness: 4 mm, gap: 15%, voxel size: 3 × 3 × 4.6 mm). For each run, 330 volumes were obtained, each containing 34 slices covering the whole brain, acquired in descending order. Anatomical images were obtained using a T1-weighted MPRAGE sequence (TR: 1900 ms, TE: 2.26 ms, flip angle: 9°, slice thickness: 1 mm, gap: 50%, voxel size: 1 × 1 × 1.5 mm).

Behavioral Data Analysis

Logistic psychometric functions were fitted to the data for each individual participant using Psignifit (Fründ et al. 2011) in Matlab. The thresholds (delay at which a 50% detection rate was reached) and slopes of the psychometric functions were extracted and used to analyze the differences between the conditions with repeated-measures ANOVAs.

The onset and offset of the movements were determined manually using the video recordings in order to calculate the durations of the movements. Paired *t*-tests were performed to test for differences in movement durations between active and passive movements.

Functional Data Preprocessing and Analysis

The functional data were analyzed using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, University College London, UK). Realignment was applied to correct for head movement. The anatomical image of each participant was coregistered to their functional scans, segmented and normalized to the standard Montreal Neurological Institute (MNI) template. The resulting parameters were then used to normalize the functional images to the MNI template (resampled to a voxel size of 2 × 2 × 2 mm). Lastly, the data were smoothed with an 8 × 8 × 8 mm^3 full-width at half maximum kernel. A general linear model (GLM) was set up for each participant to analyze the preprocessed functional data. Regressors were included for each condition (active unimodal, active bimodal, passive unimodal, and passive bimodal), modeling the 4 s in which the camera was on and during which active or passive movements were made. Trials in which participants did not perform a movement were excluded, as well as bimodal trials in which no tone was played due to issues with the movement onset detection algorithm (1.4% of all trials). Furthermore, a regressor modeling the cue was included, as well as a regressor modeling the presentation of the question until the participants answered by button press. In addition, the 6 motion parameters were included as regressors of no interest. The delay between the movement and presented visual feedback was used to parametrically modulate the regressors of the 4 experimental conditions. All regressors were convolved with the canonical haemodynamic response function (HRF). T-contrasts were created of the parametric regressors and passed on to second-level analysis using a flexible factorial design. As our primary goal was to investigate the neural correlates of comparative mechanisms specific to voluntary action, we created a T-contrast of active against passive parametric regressors (active unimodal & active bimodal > passive unimodal & passive bimodal). In addition, we explored the general effect of delay in all conditions by testing the positive correlations of delay with brain activity across conditions (all conditions together). To test for an effect of modality, we contrasted bimodal against unimodal conditions (and vice versa). Furthermore, we looked at the interaction between modality and action. The statistical threshold for whole-brain analyses was set by rejecting clusters that were smaller than could be expected by chance based on Monte Carlo

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

simulations (Slotnick 2004) using the estimated smoothness of our functional data (12.7 mm). This resulted in a minimal cluster size of 83 voxels at a threshold of $P < 0.001$ uncorrected to achieve correction for multiple comparisons for $P < 0.05$.

Results

Behavioral Results

Psychometric functions were fitted to the behavioral data, and the 50%-thresholds (point of subjective equality; PSE) and slopes were extracted. Repeated-measures ANOVAs were performed on the thresholds and slopes with the factors Action (active/passive) and Modality (unimodal/bimodal). The analysis of the thresholds revealed a significant main effect of Action ($F(1,19) = 6.779$, $P = 0.017$, $\eta^2_p = 0.263$), with lower threshold and thus better performance in passive trials (Fig. 2). The main effect of Modality was not significant ($F(1,19) = 1.091$, $P = 0.309$, $\eta^2_p = 0.054$), nor its interaction with Action ($F(1,19) = 1.345$, $P = 0.261$, $\eta^2_p = 0.066$). The slopes did not show any significant main effects (Action: $F(1,19) = 1.156$, $P = 0.296$, $\eta^2_p = 0.057$; Modality: $F(1,19) = 1.971$, $P = 0.176$, $\eta^2_p = 0.094$) or interaction ($F(1,19) = 1.283$, $P = 0.271$, $\eta^2_p = 0.063$).

Paired t-tests between the durations of active (mean: 1374 ms) and passive movements (mean: 1283 ms) showed no significant differences between the conditions ($P = 0.234$, $d = 0.340$), indicating that any differences found between active and passive conditions cannot be attributed to differences in the duration of the movement and the accompanying duration of moving visual feedback.

fMRI Results

When contrasting the active against the passive parametric regressors, we observed a significant cluster in lobule V of the right cerebellum (x, y, z = 10, −54, −16, $T = 3.96$, $k_E = 104$), in which activity correlated more strongly with delay for active compared to passive conditions (Fig. 3A). There were no significant clusters for any effects of Modality, neither for the Action × Modality interaction. The main effect of Condition (i.e., positive effect over all 4 conditions) revealed two large clusters near the bilateral temporoparietal junctions (right: x, y, z = 42, −62, 8, $T = 5.08$, $k_E = 1059$; left: x, y, z = −52, −46, 10, $T = 4.75$, $k_E = 279$), including the angular gyrus, supramarginal gyrus, superior temporal gyrus, and middle temporal gyrus (Fig. 3B).

These results suggest that the cerebellum is involved in delay detection specifically for voluntary action consequences, whereas the angular and middle temporal gyrus seem to detect more general sensory mismatches, not specific to voluntary action. However, in view of the many studies reporting a role for the angular and middle temporal gyrus in action awareness, we assumed that although these areas are correlated with delays in both active and passive conditions, they might still contribute to our awareness of action consequences. We therefore added the behavioral data in the form of the individual detection thresholds as covariates in our model, and performed a ROI analysis using anatomical masks of the angular and middle temporal gyri based on the WFU Pickatlas (Maldjian et al. 2003) and the automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al. 2002). These ROI analyses include a small volume correction for multiple comparisons, and results were viewed at a threshold of $P < 0.001$ uncorrected, with an extent threshold of 10 voxels. Since a lower detection threshold reflects better delay detection performance, we tested for negative correlations with behavior, meaning the more brain activity correlated with delay, the better the detection performance. To this end, we performed t-tests on the covariates, one contrasting passive with active covariates, testing for a more negative correlation with behavior in active than in passive conditions, and one testing a negative correlation across all conditions. The analysis showed no significant clusters when contrasting correlations in passive against correlations in active conditions, neither in the angular gyrus, nor in the middle temporal gyrus. However, we found significant negative correlations with detection thresholds across all conditions in the left angular gyrus (x, y, z = −54, −66, 24, $T = 4.70$, $k_E = 166$). In the middle temporal gyrus, 3 clusters showed significant negative correlations across all conditions (right: x, y, z = 60, −2, 10, $T = 5.48$, $k_E = 213$; left: x, y, z = −58, −36, 0, $T = 5.03$, $k_E = 173$; and x, y, z = −60, −10, −12, $T = 3.80$, $k_E = 46$). Analysis on the whole-brain level additionally revealed a significant negative correlation with detection thresholds across conditions in not only the angular and middle temporal gyrus, as found in the ROI analysis, but also in the anterior cingulate (x, y, z = −4, 46, −18, $T = 6.12$, $k_E = 1001$) and left caudate nucleus (x, y, z = −6, 0, −12, $T = 4.46$, $k_E = 86$; Fig. 4). Contrasting passive with active conditions did not yield any significant areas on the whole-brain level.

In order to further explore the role of the angular and middle temporal gyrus in action-feedback monitoring, we investigated whether these areas show functional connectivity with the cerebellum that is modulated by voluntary action. To this end, we performed a psychophysiological interaction (PPI) analysis using the cluster in the right cerebellum, identified by the

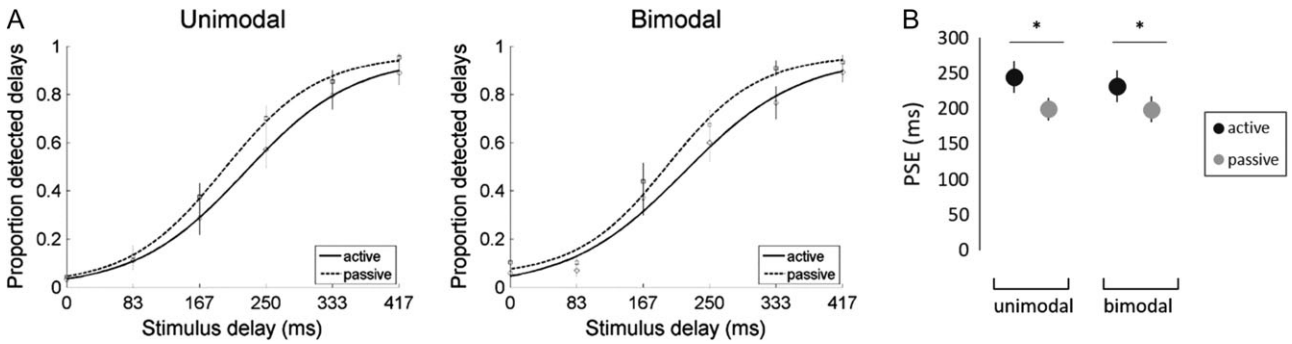

Figure 2. Behavioral results. (A) Group psychometric functions for active and passive conditions in unimodal and bimodal trials. Note that these curves were fitted over averaged data for illustration purposes; the actual analyses were done on individually fitted curves. (B) Average points of subjective equality for all conditions. Delay detection performance was significantly better in passive compared to active trials. There were no significant differences between unimodal and bimodal conditions. Error bars represent standard errors of the means (SEMs).

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

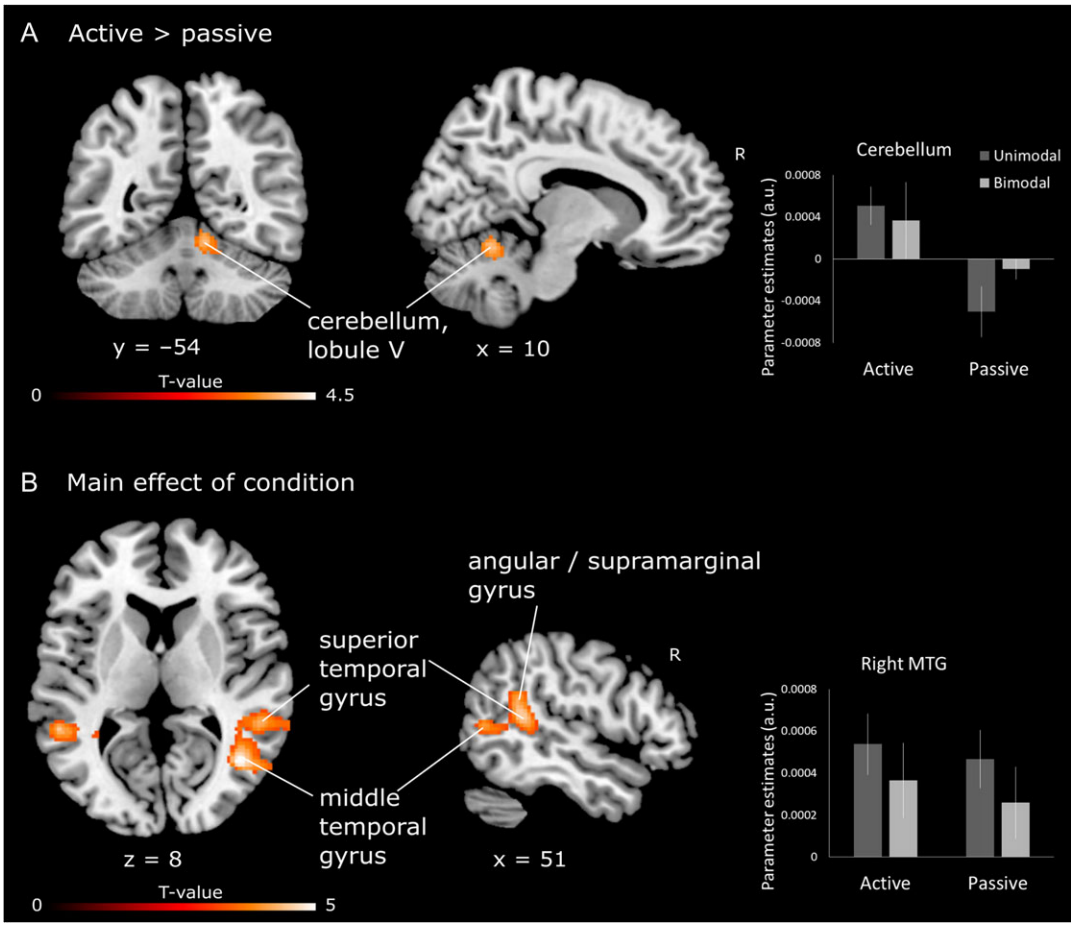

Figure 3. Group results of parametric analyses. (*A*) Activity correlating more positively with delay in active compared to passive trials is shown. (*B*) Clusters showing a significant positive correlation between activity and delay across all conditions are depicted. Bar plots illustrate the mean of extracted eigenvariates for each condition for the corresponding cluster. Error bars represent standard error of the mean (SEM). Cluster-defining threshold: $P < 0.001$, corrected for multiple comparisons using Monte Carlo simulation (minimal cluster size: 83 voxels).

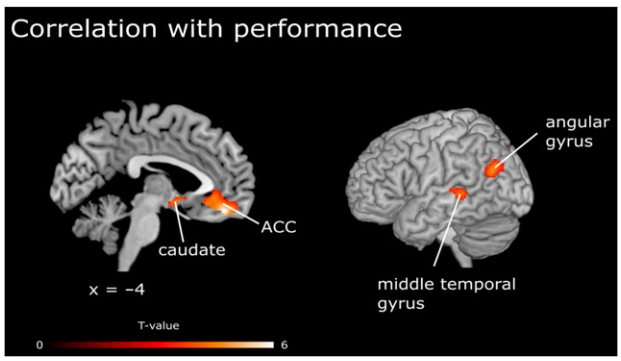

Figure 4. Correlation with behavioral performance, whole-brain analysis. The individual 50% detection thresholds (PSEs) were added as a covariate. Activity in the angular gyrus and SMA showed a significant positive correlation with performance across all conditions. Cluster-defining threshold: $P < 0.001$, extent threshold: 10 voxels, corrected for multiple comparisons (small volume correction).

contrast active >passive reported above, as a seed region. We contrasted the active against the passive PPI regressors and first performed a ROI analysis using anatomical masks of bilateral angular and middle temporal gyri from the WFU Pickatlas. This analysis showed significantly increased functional connectivity between the right cerebellum and bilateral middle temporal gyrus during active compared to passive conditions (right: *x*, *y*, *z* = 54, −72, −2, $T = 3.60$, $k_E = 57$; left: *x*, *y*, *z* = −42, −60, 12, $T = 3.63$, $k_E = 21$). With only 6 voxels in the angular gyrus ROI, this area did not reach significance. On the whole brain level, we observed significantly increased connectivity during active compared to passive conditions between the right cerebellum and motor-related areas, such as the supplementary motor area (*x*, *y*, *z* = −4, 12, 38, $T = 5.22$, $k_E = 1298$) and left primary motor cortex (*x*, *y*, *z* = −34, −8, 60, $T = 5.23$, $k_E = 1463$), extending into premotor and primary somatosensory cortex (Fig. 5). Furthermore, we found a cluster in the left thalamus (*x*, *y*, *z* = −24, −18, 12, $T = 4.42$, $k_E = 105$), two clusters bordering bilateral putamen/insula (left: *x*, *y*, *z* = −36, 2, 4, $T = 4.21$, $k_E = 85$; right: *x*, *y*, *z* = 36, 2, −2, $T = 4.02$, $k_E = 97$), and a large cluster in parietal cortex (*x*, *y*, *z* = −16, −74, 40, $T = 4.35$, $k_E = 1061$), which included bilateral precuneus, bilateral superior parietal lobule, and early visual areas around the calcarine gyrus/cuneus. Our data also revealed a main effect of Modality, where connectivity was significantly increased in bimodal compared to unimodal conditions between our seed region in right cerebellum and bilateral superior parietal lobule (left: *x*, *y*, *z* = −22, −46, 68, $T = 4.84$, $k_E = 138$; right: *x*, *y*, *z* = 26, −50, 72, $T = 3.96$, $k_E = 117$), right auditory cortex (*x*, *y*, *z* = 52, −18, 6, $T = 4.74$, $k_E = 254$), and left middle temporal gyrus/V5 (*x*, *y*, *z* = −50, −72, −2, $T = 4.49$, $k_E = 135$). There was no significant Action × Modality interaction.

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

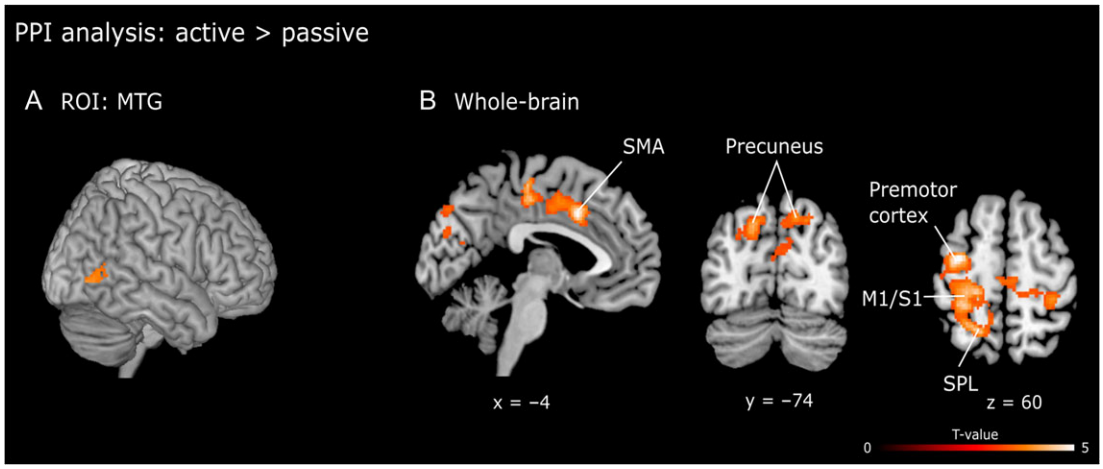

Figure 5. PPI analysis depicting areas that showed increased functional connectivity during active compared to passive trials with the seed region in right cerebellum. (A) ROI analysis with bilateral middle temporal gyrus as ROI. Cluster-defining threshold: $P < 0.001$, extent threshold: 10 voxels, corrected for multiple comparisons (small volume correction). (B) Whole-brain analysis. Cluster-defining threshold: $P < 0.001$, corrected for multiple comparisons using Monte Carlo simulation (minimal cluster size: 83 voxels).

Discussion

The current study uses for the first time both active conditions and automated passive conditions to study action-feedback monitoring in the human brain using fMRI. Our results show that activity in the right cerebellum correlated significantly more with delay in active than in passive trials, whereas activity in the angular and middle temporal gyri correlated with delay in all conditions. This suggests that the cerebellum is specifically involved in comparative processing during voluntary action, since its activity was modulated by the nature of the action (self-generated vs. externally generated). In contrast, the angular and middle temporal gyrus seem to perform matching functions that are not specific to voluntary action. However, the middle temporal gyrus showed increased functional coupling with the right cerebellum during active compared to passive trials, suggesting it might be more involved in the transmission of information about sensory mismatches with the cerebellum in voluntary action. In addition, the angular gyrus and middle temporal gyrus might contribute to our awareness of discrepancies in general, as activity in these areas showed a significant correlation with detection performance in all conditions.

Disentangling Action-based Comparisons from Intersensory Conflict Detection

Our findings provide important new insights into action–outcome monitoring by disentangling the contributions of the different areas reported in the literature. Previous studies have attributed comparator functions to the cerebellum (Blakemore et al. 2001; Diedrichsen et al. 2005; Schlerf et al. 2012), to parietal areas such as the angular gyrus (Farrer et al. 2003, 2008; Leube, Knoblich, Erb, Kircher, et al. 2003; van Kemenade et al. 2017), or to temporal areas such as the middle temporal gyrus (Leube, Knoblich, Erb, Grodd, et al. 2003; Leube et al. 2010). So far, it remained unclear what the roles of these different areas were. Since none of these studies used a passive control condition, it is difficult to say whether they measured comparator functions as proposed by the forward model, i.e., comparing predicted with actual action outcomes, or whether they measured more general matching processes, for example matching of various sensory signals such as proprioceptive, tactile, visual, and auditory signals. After all, inducing deviations between action and feedback does not only involve comparator processes, comparing predicted from actual sensory outcomes using the efference copy, but also sensory matching processes between the expected sensory signals, and general predictions about the presentation of stimuli. Indeed, Yomogida et al. found that areas in parietal and temporal cortex could be activated simply by oddball errors or sensory matching errors that are not specific to action or the feeling of agency (Yomogida et al. 2010). Furthermore, a functional near-infrared spectroscopy (fNIRS) study which included no voluntary action at all, only passively delivered stimuli, found that the inferior parietal cortex was activated by asynchronous visual-proprioceptive feedback (Shimada et al. 2005). In addition, TMS over the right temporoparietal junction disrupted intersensory conflict (Papeo et al. 2010), providing more evidence for a role of temporoparietal areas in intersensory conflict detection. These findings are supported by studies that included both active and passive movements to study intersensory conflict. For example, when comparing asynchronous with synchronous feedback, activity was found in the temporoparietal junction (Balslev et al. 2006), supramarginal and angular gyri (Tsakiris et al. 2010) for both active and passive conditions, suggesting that these areas are involved in the processing of intersensory conflict independent of the efference copy. Our results support this idea that the angular and middle temporal gyri may be involved in more general intersensory conflict detection ("intersensory conflict detection" areas), which is not specific to voluntary action, as we observed correlations with delay across both active and passive conditions. There were no significant differences in the correlation with delay between active and passive conditions in these two areas, suggesting that the correlation between activity and delay was not modulated by the nature of the action, and thus may reflect more general matching processes not based on the efference copy. In contrast, in the cerebellum we found a significant difference in the correlation with delay between active and passive conditions. Since the active condition contains both intersensory and sensorimotor conflict, and the passive condition only intersensory conflict, this difference is likely due to the efference copy. Also, this suggest that temporoparietal areas primarily process intersensory conflict, since a difference between active

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

and passive conditions could not be observed in these areas. However, it should be noted that our data cannot completely exclude the possibility that temporoparietal areas might be involved in both intersensory and sensorimotor conflict; after all, it could be there was a subtle difference between the conditions that was not observable with our methods, or that a complex interaction between intersensory and sensorimotor conflict lead to similar scaling of brain activity with delay in both the active and the passive condition. Considering the fact that we carefully matched our conditions, so that intersensory conflict would be present in both conditions, and sensorimotor conflict only in the active condition, we feel that our data speak most likely for the interpretation that the cerebellum processes sensorimotor conflict, and the angular and middle temporal gyri intersensory conflict. Nevertheless, it might be more cautious to say that our data show a differentiation between the roles of the cerebellum and temporoparietal areas in action-feedback monitoring: the cerebellum can be clearly isolated as a comparator area for sensorimotor control, whereas the angular and middle temporal gyri seem to have more broad functions, including—but potentially not limited to—intersensory conflict detection. Since we manipulated the temporal occurrence of the stimuli, our results likely reflect temporal matching processes. However, since Yomogida et al. have shown that temporoparietal areas can also be activated by semantic incongruencies or oddball errors, the function of these areas may not be limited to temporal matching only.

The role of the Cerebellum

The inclusion of a controlled passive condition, in which all sensory signals were similar to those in active trials, allowed us to identify comparator processes specific to voluntary action. We found that activity in the cerebellum correlated more strongly with delay in active compared to passive trials. These findings support previous fMRI studies that reported an involvement of the cerebellum in actively generated prediction errors (Blakemore, Wolpert, et al. 1998, 1999; Blakemore et al. 2001; Christensen et al. 2007; Schlerf et al. 2012). Since we found that the correlation with delay was modulated by the nature of the action (self-generated vs. externally generated), our results confirm that the cerebellum signals prediction errors specific to voluntary action. These findings thus suggest that the cerebellum is a "comparator" area (vs. "intersensory conflict detection" areas: angular and middle temporal gyri) in the framework of the forward model, processing sensorimotor conflict based on efference copy mechanisms. Furthermore, these results are in line with several patient studies, showing that cerebellar patients are impaired at updating predictions about sensory action consequences (Synofzik, Lindner, et al. 2008; Roth et al. 2013). In addition, our results support findings from monkey studies, showing that internal models are updated in the cerebellum (Brooks et al. 2015; Cullen and Brooks 2015).

The correlation with delay was found in lobule V of the right cerebellum. This lobule has been associated with movement and somatosensation of the right hand (Grodd et al. 2001), and has been previously reported to signal actively generated prediction errors (Diedrichsen et al. 2005; Schlerf et al. 2012). This exact location has not always been found consistently, as for example Blakemore and colleagues found correlations with delay a bit more lateral in lobule VI/Crus I (Blakemore et al. 2001). However, a cerebellar division has been suggested, with the anterior part being more important for motor functions, whereas the posterior part might be more involved in the processing of externally generated stimuli (Christensen et al. 2007). Both lobules V and VI are part of the anterior cerebellum, suggesting that this part of the cerebellum is specifically important for action-based prediction errors.

The Roles of the Angular and Middle Temporal Gyrus

Our results suggest that the angular and middle temporal gyrus perform more general temporal matching processes. This is in line with studies investigating the detection of mismatches, reporting an involvement of parietal and middle temporal areas in oddball or mismatch detection (Molholm et al. 2005; Harsay et al. 2012; Yomogida et al. 2010). These areas are thus capable of detecting mismatches in the absence of action. In our study, no specificity towards voluntary action was found in these areas. However, many studies have suggested an involvement of these areas signaling a loss of the sense of agency, which arose when predicted action outcomes did not match the actual outcomes (David et al. 2007; Farrer et al. 2008; Nahab et al. 2011), suggesting an important role in action–feedback monitoring. What are the implications of our results for the existing literature on the sense of agency? We believe the key lies in the proposed theory that the sense of agency is established in two steps (Synofzik, Vosgerau, et al. 2008). Synofzik et al. argue that although the forward model can explain the basic mechanism detecting discrepancies between predicted and actual action outcomes, it is not sufficient to explain the establishment of a sense of agency. Instead, a second mechanism would be necessary to interpret the outcome of the comparator process, using more cognitive processes to determine whether the action-feedback should be attributed to oneself or the outside world. This theory is supported by a number of studies that reported a distinction between efference-copy based comparator mechanisms and cognitive strategies. For example, it has been shown that participants might attribute an action to oneself, despite detecting temporal mismatches between action and feedback (Farrer et al. 2013). On the neural level, it has been suggested that there are two distinct networks, one comprising early or leading responses to the loss of agency, and the other later or lagging responses (Nahab et al. 2011). The leading network comprised mainly areas in the supramarginal gyrus, inferior parietal lobule and temporoparietal junction, whereas the lagging network comprised prefrontal and posterior parietal areas. This suggests that the leading network performs the first step in determining agency, namely detecting any sensory discrepancies, whereas the lagging network is involved in the more cognitive process of attributing agency based on the sensory information. This is in line with a patient study, which showed that patients with parietal lesions were impaired at mismatch detection, yet still maintained agency (Sirigu et al. 1999). In contrast, patients with prefrontal lesions correctly adapted to spatial sensory–motor discrepancies, yet failed to become aware of the mismatches (Slachevsky et al. 2001). Altogether, this suggests that temporal and inferior parietal areas are mainly responsible for the detection of temporal or spatial mismatches, whereas the conscious establishment of a sense of agency rather involves posterior parietal and prefrontal areas. Since we did not include an agency task in this study, we cannot provide any direct evidence for this two-step model. However, our results support the idea that temporoparietal areas are rather involved in the detection of sensory mismatches, which would be the first step in the establishment of agency. Future studies could include agency judgments with active and passive conditions to shed more light on

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

the role of temporoparietal areas in establishing a sense of agency.

In addition to the sensitivity to temporal mismatches, we found that activity in the angular gyrus and middle temporal gyrus correlated significantly with individual differences in delay detection performance: the stronger the correlation between activity and delay in these areas, the better the delay detection performance. This correlation was present in both active and passive trials, again supporting the findings that these areas are not specific for voluntary action. However, such an association with behavioral performance might aid in our awareness of temporal discrepancies between action and feedback. Indeed, several studies have found an involvement of parietal areas in the awareness of action consequences and a resulting feeling of agency (Farrer et al. 2008; Yomogida et al. 2010). It has to be noted, that in order to directly test whether these areas are involved in conscious detection of delays, activity should be compared for detected and undetected trials with the same delay. In our paradigm, the number of trials for each single delay would be insufficient for such an analysis. We can thus only say, that participants with better delay detection performance showed a stronger correlation between delay and brain activity in the angular and middle temporal gyrus. Although this may point towards a role for these brain areas in awareness of delays, this evidence remains indirect. Future studies will have to further investigate this question and elucidate the exact underlying mechanism of how the angular and middle temporal gyrus might contribute to action awareness. Nevertheless, the current findings suggest that these areas are not only sensitive to the physical delays, but may also contribute to delay detection performance.

Our results also suggest that the middle temporal gyrus might be specifically important for the detection of discrepancies when the movement is self-generated, since this area showed increased connectivity with the cerebellum in active compared to passive trials. This increased communication between the two areas during voluntary action suggests that the middle temporal gyrus is involved in the transmission of information about sensory mismatches with the cerebellum, potentially aiding in the generation of prediction error signals. Indeed, an intrinsic connectivity exists between the sensorimotor zones in the cerebellum (primarily lobules V and VI) and visual area MT, located in the middle temporal gyrus (Reilly et al. 2010). How this connectivity might contribute exactly to prediction error generation remains an open question for future studies. Furthermore, it should be noted we could not identify the effect of delay on functional connectivity with the MTG, since our design was not optimized for such an analysis, leaving an insufficient number of trials per delay. Our interpretation that the MTG is involved in the transmission of information about delays is thus based on indirect evidence. Nevertheless, the fact that connectivity was increased specifically during active conditions suggests a specificity in the communication transfer between the cerebellum and MTG during voluntary action.

Behavioral Effects

Our results showed reduced delay detection performance in active compared to passive conditions. This is in line with studies reporting reduced perceptual performance for self-generated stimuli compared to externally generated stimuli, often referred to as sensory suppression or attenuation (Blakemore et al. 2000). For example, the intensity of self-generated stimuli is often perceived as less intense than externally generated stimuli. Such reduced sensitivity has been reported for the tactile (Blakemore, Frith, et al. 1999), visual (Cardoso-leite et al. 2010), and auditory modality (Weiss et al. 2011). On the neural level, this effect has been accompanied by reduced neural responses to the self-generated stimuli as measured by EEG or fMRI (Blakemore et al. 1998; Martikainen et al. 2005; Straube, van Kemenade, Arikan, et al. 2017). These effects are explained by the forward model framework as a result of efference-copy based predictions: self-generated stimuli can be predicted, and when our predictions match the actual sensory stimuli, the stimuli are therefore less surprising than externally generated stimuli. In that case, less resources are allocated to the processing of self-generated stimuli, freeing up resources to process unpredicted stimuli (Wolpert and Flanagan 2001). In the current study, we found reduced delay detection performance, pointing towards less accurate temporal processing. In view of the mentioned studies, we interpret this as evidence for sensory attenuation of self-generated stimuli. However, it should be noted that several studies—including our own studies—have rather found an opposite effect of the efference copy, and reported enhanced behavioral performance or neural processing (Shimada et al. 2010; Ackerley et al. 2012; Reznik et al. 2015; Schmalenbach et al. 2017; van Kemenade et al. 2016). The different results in our studies might be due to the fact that the feedback and movement types differed in our studies: those in which we found enhancement used button presses as action and abstract, discrete sensory consequences (tone or dot on the screen at the end of a button press), whereas the current study used a longer wrist movement as action and natural, continuous feedback (video recording of one's own hand during the whole movement). It has been reported that participants are more sensitive to discrete action outcomes compared to continuous feedback (David et al. 2016), which is in line with our findings, and with those by Reznik et al., who also used discrete action outcomes. However, this does not explain the enhancement effects in the studies by Shimada et al. and Ackerley et al., in which continuous natural feedback was provided. It might be that other factors such as the type of movement play a role as well; Shimada and colleagues used button presses, as we did in our experiment that reported better performance in active conditions (van Kemenade et al. 2016). Future research should aim to tease apart the contributions of feedback type and movement type to fully understand these heterogeneous reports.

The Role of Movement Complexity and Exogenous Attention

Two factors that should be considered when comparing active with passive movements are firstly a potential difference in the complexity of performing active compared to passive movements, and secondly potential differences in exogenous attention when delaying visual feedback. Concerning movement complexity, it is important to note that the movement trajectories themselves did not differ, since our device only allowed movements along a predefined axis in both active and passive conditions (see Fig. 1A). Posthoc analyses also revealed no differences in movement duration. However, in active movements, participants were required to move the device at the trained speed. In passive trials, their hand was being moved by the device, so no additional speed monitoring was required. Potentially, due to the speed monitoring in active trials, there were less resources left to detect delays. We do not think that this could explain the result, since speed monitoring requires participants to pay close attention to the visual feedback, and correct for any minute deviations. Delays should

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

therefore be rather more conspicuous in the active conditions. Concerning exogenous attention, we aimed to make active and passive conditions as equal as possible, by (1) giving participants the exact same task in each condition, namely detecting delays between hand movement and shown video image, (2) fixing the movement trajectories, to keep movement dynamics the same, (3) providing the same sensory feedback in each condition, and (4) training participants extensively prior to the scanning session. Nevertheless, we cannot completely rule out that exogenous attention may have differed between active and passive conditions. However, our neural data speak against this possibility. The temporoparietal areas that we found, of which some may overlap with areas involved in exogenous attention, showed a correlation between BOLD signal and delay for both active and passive conditions. The area that did show differences between active and passive conditions when considering delay detection was the cerebellum, which is not associated with exogenous attention. It is thus unlikely that exogenous attention differed between active and passive conditions, and thus the behavioral differences between active and passive conditions are better explained by sensory attenuation effects.

Multisensory Effects

The addition of tones as sensory outcomes did not affect behavioral performance, as there was no significant difference in thresholds or slopes between unimodal and bimodal conditions. This is in contrast with the previously reported bimodal advantage in the detection of delays between action and feedback (van Kemenade et al. 2016, 2017; Schmalenbach et al. 2017; Straube, van Kemenade and Arikan et al. 2017). However, these previous studies used discrete stimuli that were presented after a button press, i.e., at the end of the action, thus representing an action outcome. In the current study, feedback of the hand was continuously provided via video camera throughout the whole movement. A recent study by David et al. (2016) found that participants were more sensitive to action outcomes than to continuous action feedback. It could therefore be the case that a bimodal advantage is particularly present with discrete action outcomes, and less with continuous action feedback, to which participants are generally less sensitive. On the neural level, we observed no significant differences in the correlation with delay between unimodal and bimodal conditions, suggesting that the processing of unimodal and bimodal action consequences relies on the same mechanism. This is congruent with our previous finding that bimodal action consequences led to suppression of neural activity in the same areas as unimodal consequences (Straube, van Kemenade, Arikan, et al. 2017). The only case in which we found differences between unimodal and bimodal conditions is in our functional connectivity analysis, which showed increased connectivity in bimodal conditions between the right cerebellum and visual cortex, auditory cortex, and the superior parietal lobule. This effect was present for both active and passive conditions, suggesting this connectivity pattern is action-independent. Indeed, previous studies have reported involvement of the cerebellum in purely perceptual tasks (Bastian 2012; Baumann et al. 2015), especially tasks requiring precise timing (Ivry and Spencer 2004; O'Reilly et al. 2008). Functional connectivity between the cerebellum and sensory areas has been reported previously, for example during resting state (Reilly et al. 2010; Kipping et al. 2013), during a temporal task (O'Reilly et al. 2008), and during multisensory action-outcome processing (Straube, van Kemenade, Arikan, et al. 2017). Our findings could thus reflect an increased usage of temporal information from sensory and multisensory integration areas during bimodal trials. Nevertheless, there was no difference between parametrically modulated unimodal and bimodal trials in the cerebellum, or any other brain region for that matter. Thus, even when the cerebellum communicated more strongly with sensory areas during bimodal trials, it did not influence the comparative function of the cerebellum. This suggests that prediction errors are signaled in a similar way for unimodal and bimodal action consequences. It should be noted though, that in order to fully understand potential supramodal mechanisms, a unimodal auditory condition would be necessary, to identify brain areas that process action consequences in both the visual and the auditory modality. Since this is beyond the scope of the current study, this condition was not added to allow for more trials for the main conditions. Future studies could include unimodal visual and unimodal auditory conditions to identify supramodal mechanisms.

Conclusions

All in all, we were able to disentangle action-based comparative processes from general temporal mismatch processes, thereby showing that the cerebellum is specifically involved in comparator processes during voluntary action for both unimodal and bimodal action feedback. In contrast, the angular and middle temporal gyrus were rather involved in general intersensory conflict detection. Although a possible role in sensorimotor conflict cannot be completely ruled out for the angular and middle temporal gyri, these areas did not show any difference between the active and passive condition, and thus seem to lack specificity for sensorimotor conflicts in voluntary action. However, the middle temporal gyrus showed increased connectivity with the cerebellum in active compared to passive trials, suggesting a communication transfer particularly relevant in voluntary action. In addition, the activity of the angular and middle temporal gyrus correlated with delay detection thresholds across all conditions, supporting the idea that the angular and middle temporal gyrus contribute to awareness of temporal discrepancies. These novel findings clarify the role of these areas and provide the first step towards a more comprehensive framework of action outcome monitoring.

Funding

This study was funded by the "Deutsche Forschungsgemeinschaft" (DFG) through the SFB/Transregio 135, "Cardinal mechanisms of perception: prediction, valuation, categorization", and through the International Research Training Group, IRTG 1901, "The Brain in Action-BrainAct". B.S. is supported by Deutsche Forschungsgemeinschaft grants STR 1146/8-1 and STR 1146/9-1.

Notes

We thank Jens Sommer for technical support, Christina Lubinus for assistance with data collection, and Inessa Kraft for assistance with data analysis. The data are available at 10.5281/zenodo.1172689. *Conflict of Interest*: The authors declare no competing financial interests.

References

Ackerley R, Hassan E, Curran A, Wessberg J, Olausson J, Mcglone F. 2012. An fMRI study on cortical responses during active self-touch and passive touch from others. Front Behav Neurosci. 6:1–9.

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

Balslev D, Nielsen FÅ, Lund TE, Law I, Paulson OB. 2006. Similar brain networks for detecting visuo-motor and visuo-proprioceptive synchrony. NeuroImage. 31:308–312.

Bastian AJ. 2012. Moving, sensing and learning with cerebellar damage. Curr Opin Neurobiol. 21(4):596–601.

Baumann O, Borra RJ, Bower JM, Cullen KE, Habas C, Ivry RB, Leggio M, Mattingley JB, Molinari M, Moulton EA, et al. 2015. Consensus paper: the role of the cerebellum in perceptual processes. Cerebellum. 14:197–220.

Blakemore S, Frith CD, Wolpert DM. 1999a. Spatio-temporal prediction modulates the perception of self-produced stimuli. J Cogn Neurosci. 11(5):551–559.

Blakemore SJ, Frith CD, Wolpert DM. 2001. The cerebellum is involved in predicting the sensory consequences of action. NeuroReport. 12(9):1879–1884.

Blakemore S, Sirigu A. 2003. Action prediction in the cerebellum and in the parietal lobe. Exp Brain Res. 153:239–245.

Blakemore SJ, Wolpert DM, Frith CD. 1998. Central cancellation of self-produced tickle sensation. Nat Neurosci. 1(7):635–640.

Blakemore SJ, Wolpert DM, Frith CD. 1999b. The cerebellum contributes to somatosensory cortical activity during self-produced tactile stimulation. NeuroImage. 10:448–459.

Blakemore SJ, Wolpert D, Frith C. 2000. Why can't you tickle yourself? NeuroReport. 11(11):11–16.

Brooks JX, Carriot J, Cullen KE. 2015. Learning to expect the unexpected: rapid updating in primate cerebellum during voluntary self-motion. Nat Neurosci. 18(9):1310–1319.

Cardoso-leite P, Mamassian P, Schütz-Bosbach S, Waszak F. 2010. A new look at sensory attenuation: action-effect anticipation affects sensitivity, not response bias. Psychol Sci. 21 (12):1740–1745.

Christensen MS, Lundbye-jensen J, Petersen N, Geertsen SS, Paulson OB, Nielsen JB. 2007. Watching your foot move—an fMRI study of visuomotor interactions during foot movement. Cereb Cortex. 17(8):1906–1917.

Cullen KE, Brooks JX. 2015. Neural correlates of sensory prediction errors in monkeys: evidence for internal models of voluntary self-motion in the cerebellum. Cerebellum. 14:31–34.

David N, Cohen MX, Newen A, Bewernick BH, Shah NJ, Fink GR, Vogeley K. 2007. The extrastriate cortex distinguishes between the consequences of one's own and others' behavior. NeuroImage. 36:1004–1014.

David N, Skoruppa S, Gulberti A, Schultz J, Engel AK. 2016. The sense of agency is more sensitive to manipulations of outcome than movement-related feedback irrespective of sensory modality. PLoS One. 11(8):1–12.

Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R. 2005. Neural correlates of reach errors. J Neurosci. 25(43):9919–9931.

Farrer C, Franck N, Georgieff N, Frith CD, Decety J, Jeannerod M. 2003. Modulating the experience of agency: a positron emission tomography study. NeuroImage. 18:324–333.

Farrer C, Frey SH, Van Horn JD, Tunik E, Turk D, Inati S, Grafton ST. 2008. The angular gyrus computes action awareness representations. Cereb Cortex. 18:254–261.

Farrer C, Frith CD. 2002. Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. NeuroImage. 15:596–603.

Farrer C, Valentin G, Hupé JM. 2013. The time windows of the sense of agency. Conscious Cogn. 22:1431–1441.

Fründ I, Haenel NV, Wichmann F. 2011. Inference for psychometric functions in the presence of nonstationary behavior. J Vis. 11(6):1–19.

Grodd W, Hülsmann E, Lotze M, Wildgruber D, Erb M. 2001. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. Hum Brain Mapp. 13: 55–73.

Harsay HA, Spaan M, Wijnen JG, Ridderinkhof KR. 2012. Error awareness and salience processing in the oddball task: shared neural mechanisms. Front Hum Neurosci. 6:1–20.

Ivry RB, Spencer RMC. 2004. The neural representation of time. Curr Opin Neurobiol. 14:225–232.

Khalighinejad N, Haggard P. 2015. Modulating human sense of agency with non-invasive brain stimulation. Cortex. 69: 93–103.

Kipping JA, Grodd W, Kumar V, Taubert M, Villringer A, Margulies DS. 2013. Overlapping and parallel cerebello-cerebral networks contributing to sensorimotor control: an intrinsic functional connectivity study. NeuroImage. 83: 837–848.

Leube DT, Knoblich G, Erb M, Grodd W, Bartels M, Kircher TTJ. 2003a. The neural correlates of perceiving one's own movements. NeuroImage. 20:2084–2090.

Leube DT, Knoblich G, Erb M, Kircher TTJ. 2003b. Observing one's hand become anarchic: an fMRI study of action identification. Conscious Cogn. 12:597–608.

Leube DT, Knoblich G, Erb M, Schlotterbeck P, Kircher TTJ. 2010. The neural basis of disturbed efference copy mechanism in patients with schizophrenia. Cogn Neurosci. 1(2):111–117.

Maldjian JA, Laurienti PJ, Burdette JH, Kraft RA. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage. 19: 1233–1239.

Martikainen MH, Kaneko K, Hari R. 2005. Suppressed responses to self-triggered sounds in the human auditory cortex. Cereb Cortex. 15:299–302.

Miall RC, Wolpert DM. 1996. Forward models for physiological motor control. Neural Netw. 9(8):1265–1279.

Molholm S, Martinez A, Ritter W, Javitt DC, Foxe JJ. 2005. The neural circuitry of pre-attentive auditory change-detection: an fMRI study of pitch and duration mismatch negativity generators. Cereb Cortex. 15:545–551.

Nahab FB, Kundu P, Gallea C, Kakareka J, Pursley R, Pohida T, Miletta N, Friedman J, Hallett M. 2011. The neural processes underlying self-agency. Cereb Cortex. 21:48–55.

O'Reilly JX, Mesulam MM, Nobre AC. 2008. The cerebellum predicts the timing of perceptual events. J Neurosci. 28(9): 2252–2260.

Papeo L, Longo MR, Feurra M, Haggard P. 2010. The role of the right temporoparietal junction in intersensory conflict: detection or resolution? Exp Brain Res. 206:129–139.

Reilly JXO, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. 2010. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb Cortex. 20:953–965.

Reznik D, Ossmy O, Mukamel XR. 2015. Enhanced auditory evoked activity to self-generated sounds is mediated by primary and supplementary motor cortices. J Neurosci. 35(5): 2173–2180.

Roth MJ, Synofzik M, Lindner A. 2013. The cerebellum optimizes perceptual predictions about external sensory events. Curr Biol. 23(10):930–935.

Schlerf J, Ivry RB, Diedrichsen J. 2012. Encoding of sensory prediction errors in the human cerebellum. J Neurosci. 32(14): 4913–4922.

Schmalenbach SB, Billino J, Kircher T, van Kemenade BM, Straube B. 2017. Links between gestures and multisensory processing: individual differences suggest a compensation mechanism. Front Psychol. 8:1828.

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018

Shimada S, Hiraki K, Oda I. 2005. The parietal role in the sense of self-ownership with temporal discrepancy between visual and proprioceptive feedbacks. NeuroImage. 24:1225–1232.

Shimada S, Qi Y, Hiraki K. 2010. Detection of visual feedback delay in active and passive self-body movements. Exp Brain Res. 201:359–364.

Sirigu A, Daprati E, Pradat-diehl P, Franck N, Jeannerod M. 1999. Perception of self-generated movement following left parietal lesion. Brain. 122:1867–1874.

Slachevsky A, Pillon B, Fourneret P, Pradat-diehl P, Jeannerod M, Dubois B. 2001. Preserved adjustment but impaired awareness in a sensory-motor conflict following prefrontal lesions. J Cogn Neurosci. 13(3):332–340.

Slotnick SD 2004. Cluster_threshold. Retrieved October, 24, 2016 from http://www2.bc.edu/~slotnick.scripts.htm

Sperry RW. 1950. Neural basis of the spontaneous optokinetic response produced by visual inversion. J Comp Physiol Psychol. 43(6):482–489.

Straube B, Schülke R, Drewing K, Kircher T, van Kemenade BM. 2017. Hemispheric differences in the processing of visual consequences of active vs. passive movements: a transcranial direct current stimulation study. Exp Brain Res. 235(10):3207–3216.

Straube B, van Kemenade BM, Arikan BE, Fiehler K, Leube DT, Harris LR, Kircher T. 2017. Predicting the multisensory consequences of one's own action: BOLD suppression in auditory and visual cortices. PLoS One. 12(1):e0169131.

Synofzik M, Lindner A, Thier P. 2008. The cerebellum updates predictions about the visual consequences of one's behavior. Curr Biol. 18:814–818.

Synofzik M, Vosgerau G, Newen A. 2008. Beyond the comparator model: a multifactorial two-step account of agency. Conscious Cogn. 17:219–239.

Tsakiris M, Longo MR, Haggard P. 2010. Having a body versus moving your body: neural signatures of agency and body-ownership. Neuropsychologia. 48(9):2740–2749.

Tseng Y, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. 2007. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. J Neurophysiol. 98:54–62.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage. 15:273–289.

van Kemenade BM, Arikan BE, Kircher T, Straube B. 2016. Predicting the sensory consequences of one's own action: first evidence for multisensory facilitation. Atten Percept Psychophys. 78(8):2515–2526.

van Kemenade BM, Arikan BE, Kircher T, Straube B. 2017. The angular gyrus is a supramodal comparator area in action – outcome monitoring. Brain Struct Funct. 222(8):3691–3703. https://doi.org/10.1007/s00429-017-1428-9.

von Holst E, Mittelstaedt H. 1950. Das Reafferenzprinzip. Wechselwirkungen zwischen Zentralnervensystem und Periphase. Die Naturwissenschaften. 37(20):464–476.

Weiss C, Herwig A, Schütz-Bosbach S. 2011. The self in action effects: selective attenuation of self-generated sounds. Cognition. 121:207–218.

Wolpert DM, Diedrichsen J, Flanagan JR. 2011. Principles of sensorimotor learning. Nat Rev Neurosci. 12:739–751.

Wolpert DM, Flanagan JR. 2001. Motor prediction. Curr Biol. 11: R729–R732.

Wolpert DM, Ghahramani Z. 2000. Computational principles of movement neuroscience. Nat Neurosci. 3:1212–1217.

Wolpert DM, Goodbody SJ, Husain M. 1998. Maintaining internal representations: the role of the human superior parietal lobe. Nat Neurosci. 1(6):529–533.

Yomogida Y, Sugiura M, Sassa Y, Wakusawa K, Sekiguchi A, Fukushima A, Takeuchi H, Horie K, Sato S, Kawashima R. 2010. The neural basis of agency: an fMRI study. NeuroImage. 50:198–207.

Downloaded from https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy048/4975476
by UB Marburg user
on 19 April 2018